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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/502,283	02/11/2000	Sun Ai Raillard	70123.210US	4948

30560 7590 12/12/2007

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EXAMINER	
EPPERSON, JON D	
ART UNIT	**PAPER NUMBER**
1639	

MAIL DATE	DELIVERY MODE
12/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/502,283	RAILLARD ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-6,23-26,72,73,77,78,106-109,115-119 and 125-143* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *3,26,72,73,77,106,115,119,125 and 127-143* is/are allowed.

6)☒ Claim(s) *4-6,23-25,78,107-109,116-118 and 126* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/16/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. The Response filed October 18, 2007 is acknowledged. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior office action.

Status of the Claims

2. Claims 3-6, 23-26, 72, 73, 77, 78, 106-109, 115-119 and 125-144 were pending. Applicants amended claims 115 and canceled claim 144. Therefore, claims 3-6, 23-26, 72, 73, 77, 78, 106-109, 115-119 and 125-143 are pending and examined on the merits.

Priority/Specification

3. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

This application claims benefit of and priority to USSN 60/119,766, "High Throughput Mass Spectrometry," by Raillard, filed February 11, 1999; USSN 60/148,848 entitled "Evolution and Use of Enzymes for Combinatorial and Medicinal Chemistry," by Liu et al., filed August 12, 1999 (e.g., see 10/18/07 amendment to specification). However, one or more of the applications stated above fail to provide adequate support under 35 U.S.C. § 112, first paragraph for the claimed invention as follows:

> (A) For ***claims 4-6, 23-25, 78, 107-109, 116-118, and 126***, the '766 application additionally fails to provide support for "neutral" loss mass spectrometry in claims 23-25 and 116-118. The '766 application also fails to provide support for "pooling" samples as set forth in claims 78 and 126.

The '766 application also fails to disclose sample rates > 100/hour as set forth, for example, in claims 4-6.

(B) For ***claims 3-6, 23-26, 72, 73, 77, 78, 107-109, 127-134, and 143***, the '848 application additionally fails to provide support for the "carbohydrate" analytes recited in independent claim 127. The '848 application also fails to provide support for the volatile buffers as set forth in claims 134 and 143. The '848 application also fails to disclose sample rates > 100/hour as set forth, for example, in claims 4-6.

Therefore, the earliest effective filing date for claims 4-6, 23-25, 78, and 107-109 is deemed to be the filing date of ***February 11, 2000*** for the present application because support for the aforementioned limitations cannot be found in either '766 or '848. Furthermore, the earliest effective filing date for claims 116-118, and 126 is deemed to be ***August 12, 1999*** because the '766 application does not fully support this claim. All other claims (i.e., claims 3, 26, 72, 73, 77, 106-109, 115, 119, 125, and 127-143) receive a priority date of ***February 11, 1999*** for '766.

Response

4. Applicant's arguments directed to the above denial of priority were considered but were not found completely persuasive. Please note that the above priority section has been modified from its original version to reflect the position outlined below.

Applicants argue that support for the currently claimed invention can be found in the priority documents and cite a plethora of passages in support of this position (e.g., see 10/18/07 Response, section III starting on page 10 and section Vb starting on page 21).

The Examiner agrees in part and the above priority section has been modified to reflect this change. The New Matter rejection has been withdrawn in view of Applicants' arguments (see above) and thus the denial of priority on this basis with respect to the priority documents is

also withdrawn for the same reasons. The objection to a lack of support for "tandem" mass spectrometry with regard to the '848 application is also withdrawn because the '848 application sets forth the use of tandem mass spectrometer such as in figure 17 wherein MS/MS detection is disclosed (i.e., MS/MS = tandem mass spectrometry). However, the objection with regard to the use of "neutral" loss mass spectrometry for the '766 application is maintained because Applicants have not provide any citation for this limitation in the '766 application. Likewise, the use of "pooling" is only referred to in the '848 application, not the '766 application. Applicants have also failed to show support for the "carbohydrate" limitation in the '848 priority document. Applicants only refer to the '766 application. The same is true for the "volatile buffers" limitation which only refers to the '848 application. In addition, Applicants have not pointed to anything other than screening approximately 100 samples/hour (e.g., see 10/18/07 Response, page 10, section IIIA, claim 3 wherein "about 100 samples per hour or more" is quoted, which does not provide support for at least about 200, 500, etc.).

Accordingly applicant's request for priority is denied in part.

Withdrawn Objections/Rejections

5. The objection to claim 115 is withdrawn in view of Applicants' amendments thereto. The rejection denoted "A" under 35 U.S.C. § 112, second paragraph is withdrawn in view of Applicants' cancellation of claim 144. The new matter rejection under 35 U.S.C. § 112, first paragraph is withdrawn in view of Applicants' citations and/or sections related thereto (e.g., see 10/18/07 Response, pages 10-21). For example, support for, "wherein the components of interest has not undergone chromatographic separation prior to step (iv)" could be found in

equivalent language at page 32, lines 4-11, "Instead of a chromatographic separation step, the samples are cleaned up with extraction methods to get rid of proteins, nucleic acids, general cell junk, and debris .... The methods used are viable for many components, including but not limited to sugars, peptides, polynucleotides, small inorganic molecules, polkyketides, beta-lactam antibiotics, triazine derivatives, and the like." Other sections cited by Applicants also provide support as cited in their response (e.g., see 10/18/07 Response, pages 10-21 and pages 21 and 22). All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claims Rejections - 35 U.S.C. 102

6. Claims 78 and 126 are rejected under 35 U.S.C. 102(e) as being anticipated by Stemmer et al. (U.S. Patent No. 6,500,617 B1) (Filed **April 22, 1999**) as evidenced by provisional application 60/119,766 (filed **February 11, 1999**). Please also note the priority section above for the current determination of the earliest effective filing date for the present claims.

For ***claims 78 and 126***, Stemmer et al. (see entire document) disclose a method of performing high throughput mass spectrometry screening (e.g., see column 53, second full paragraph, "A high throughput method for detecting analyte molecules from a complex biological matrix is by electrospray tandem mass spectrometry"). Furthermore, Stemmer et al. disclose a method that comprises providing cells that have been transfected or transformed with one or more members of library of related genes (e.g., see column 53, first full paragraph, "In one aspect, library members e.g., cells ... produce individual colonies ... and 10,000 different mutants inoculated into 96 well microtiter

dishes"). In addition, Stemmer et al. disclose growing the cells in vitro in biological matrix to express said members of the library of related genes (e.g., see column 53, first full paragraph disclosing "culture medium" as the matrix; see also column 46, line 36; see also Example 10, especially lines 50-62, "pools of the transformed cells are grown in each well). In addition, Stemmer et al. disclose separating the cells or cell debris thereof from one or more component of interest using centrifugation or filtration in parallel fashion to provide samples (e.g., see column 53, second full paragraph disclosing the filtration/centrifugation method set forth in the '766 Raillard application; e.g., see also '766 application, pages 21-23, section VI; especially page 22, paragraphs 1-3; disclosing filtration and/or centrifugation techniques). Stemmer et al. also disclose performing flow injection analysis using electrospray tandem mass spectrometry on the samples from step iii to obtain mass to charge ratio data for the component of interest wherein the component of interest (e.g., see column 53, second full paragraph). In addition, Stemmer et al. also disclose a component use of a component of interest selected from the group consisting of an inorganic ion, secondary metabolite, protein binding molecule, carbohydrate, carbohydrate binding molecule, an enzyme, an enzyme substrate product of an enzyme catalyzed reaction, nucleic acid and product of nucleic acid catalyzed reaction (e.g., see Example 7 wherein a protease inhibitor i.e., a protein binding molecule is disclosed; see also abstract and examples wherein "protein binding" toxin molecules are disclosed). Finally, Stemmer et al. disclose methods wherein the component of interest has not undergone chromatographic separation prior to step iv (e.g., see Example 10; see also column 53, second full paragraph; see also '766 application, section VI as noted

above; see also summary of invention). In addition, Stemmer et al. disclose providing cells that have been transfected or transformed with one or more members of library of related enzyme encoding genes (e.g., see column 33, line 54; see also column 51, line 38). Additionally, for claims 78 and 126, Stemmer et al. disclose up to 100 samples are pooled before performing flow injection analysis using electrospray tandem mass spectrometry (e.g., see Stemmer et al., column 36, lines 46-48).

Response

7. Applicant's arguments directed to the above 35 U.S.C. § 102 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection might have been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue, "the effective 102(e) date for [Stemmer et al.] ... is April 22, 1999 ... in view of the fact that Applicants have a priority claim to USSN 60/119,776 and all of the relevant disclosure from the Stemmer '617 patent is derived from its reference to USSN 60/119,776, the stemmer '617 patent cannot anticipate the pending claims" (e.g., see 10/18/07 Response, pages 23 and 24).

The above rejection has been amended to include only claims 78 and 126 in view of Applicants' arguments. These claims were afforded a February 11, 2000 priority date. Thus, Applicants' argument is moot (i.e., April 22, 1999 is before February 11, 2000). In addition, the

'776 application is not the only relevant disclosure as erroneously purported. For example, the Stemmer et al. disclose the concept of pooling (e.g., see Stemmer, column 36, lines 46-48), which is not described in the '776 application.

Accordingly, the 35 U.S.C. § 102 rejection cited above is maintained in part.

Claim Rejections - 35 USC § 103

8. Claims 4-6, 23-25, 78, 107-109, 116-118 and 126 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stemmer et al. (U.S. Patent No. 6,500,617 B1) (Filed **April 22, 1999**) in view of Favretto et al. (Fabretto et al. "MS/MS applications in biological problems" Mass Spectrometry Reviews **1993**, *12*, 313-395) as evidenced by provisional application 60/119,766 (filed **February 11, 1999**). Please also note the priority section above for the current determination of the earliest effective filing date for the present claims.

For ***claims 78 and 126***, Stemmer et al. teach all the limitations stated in the 35 U.S.C. 102(b) rejection above (incorporated in its entirety herein by reference), which anticipates and, as a result, renders obvious claims 3, 7, 72, 73, 78, 106, 125-134, and 136-144. *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983) ("anticipation is the epitome of obviousness"); see also *In re Skoner*, 517 F.2d 947, 950, 186 USPQ 80, 83 (CCPA 1975); *In re Pearson*, 494 F.2d 1399, 1402, 181 USPQ 641, 644 (CCPA 1974).

The prior art teaching of Stemmer et al. differ from the claimed invention as follows:

For ***claims 4-6 and 107-109***, Stemmer et al. fail to disclose at least about 200,

500, or 1000 samples are screened for presence of the one or more component of interest in less than an hour/day. Stemmer et al. only disclose 100 samples/hour (see above). However, 100 samples hour would equate to 2,400 samples/day if allowed to run for a 24-hour period, which would render obvious claims 6 and 109. In addition, the Examiner notes "the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA1955). Also note that optimization of process steps, especially with respect to numbers of samples analyzed or numbers of substrate regions is within the routine skill of the art. *In re Burhans*, 154 F.2d 690, 69 USPQ330 (CCPA 1946) (selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results). With respect to the repetition of steps (i.e. number of samples analyzed or number of substrate regions), see *In re Harza*, (274 F.2d 669, 124 USPQ 378 (CCPA 1960)) where the court held that mere duplication of parts has no patentable significance unless a new and unexpected result is produced. Here, the mere increase in sample rate would not be inventive absent some showing of unexpected results.

For ***claims 23 and 116***, Stemmer et al. fail to disclose performing flow injection analysis using electrospray tandem mass spectrometry performing method selected from the group consisting of neutral loss mass spectrometry and parent ion mass spectrometry

For ***claims 24 and 117***, Stemmer et al. fail to disclose comprising performing the neutral loss mass spectrometry or the parent ion mass spectrometry on triple quadrupole mass spectrometer

For ***claim 25***, Stemmer et al. fail to disclose performing the neutral loss mass spectrometry scanning the one or more component of interest in first quadrupole at specified mass range fragmenting the one or more component of interest in second quadrupole by collision induced dissociation thereby producing one or more neutral fragments and one or more daughter ion and detecting the one or more daughter ion

For ***claim 118***, Stemmer et al. fail to disclose performing the neutral loss mass spectrometry scanning the product of the enzymatic reaction and/or enzyme substrate in first quadrupole at specified mass range fragmenting the product of the enzymatic reaction and/or enzyme substrate in second quadrupole by collision induced dissociation thereby producing one or more neutral Fragments and one or more daughter ion and detecting the one or more daughter ion

However, Favretto et al. teach the following limitations that are deficient in Stemmer et al.:

For ***claim 23 and 116***, Favretto et al. disclose performing flow injection analysis using electrospray tandem mass spectrometry performing method selected from the group consisting of neutral loss mass spectrometry and parent ion mass spectrometry (e.g., see page 320, last paragraph; se also page 333, first full paragraph; see also page 338, first paragraph; see also figure 16; see also page 339, first full paragraph; see also page 342, last paragraph; see also page 343, first full paragraph; see also page 348, second to last paragraph; see also page 355, Pharmacology and Toxicology section; see also Lipid section starting on page 362; see also page 365, Hybrid Instruments section; see also Table II, etc. wherein "neutral loss" is disclosed).

For ***claims 24 and 117***, Favretto et al. disclose comprising performing the neutral loss mass spectrometry or the parent ion mass spectrometry on triple quadrupole mass spectrometer (e.g., see page 322-325, starting with "Triple Quadrupole Instruments" section; see also page 351, second full paragraph; see also page 354, Nucleic Acids Constituents section; see also page 380, paragraph 1, etc.).

For ***claims 25 and 118***, Favretto et al. disclose performing the neutral loss mass spectrometry scanning the one or more component of interest in first quadrupole at specified mass range fragmenting the one or more component of interest in second quadrupole by collision induced dissociation thereby producing one or more neutral fragments and one or more daughter ion and detecting the one or more daughter ion (e.g., see page 345, second paragraph in Natural Products section, MS/MS analyses ... under different conditions (FAB, DCI, low- and high-energy CID"; see also page 359, second full paragraph; see also page 368, paragraph 1; see also Triple Quadrupole Instruments" section noted above).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use "neutral loss" techniques disclosed by Favretto et al. to examined the libraries as set forth by Stemmer et al. because Favretto et al. explicitly state that their MS/MS applications can be used in biological systems (e.g., see title and introduction), which would include the proteins and/or ligand disclosed by Stemmer et al. Furthermore, a person of ordinary skill in the art would have been motivated use these "neutral loss" techniques because Favretto et al. state that this technique is particularly valuable for the identification of analytes in "complex mixtures" (e.g., see Favretto et al.,

page 333, first full paragraph). The "neutral loss" technique also reveals functionalities and/or substructures of the original analyte for in depth characterization (e.g., see Favretto et al., page 338, paragraph 1). Finally, a person of ordinary skill in the art would reasonably have expected to be successful because Favretto et al. state that these techniques can be applied to biological systems including proteins, peptides, nucleic acids, lipids and small molecules (e.g., see Favretto et al., "Peptides" section starting on page 367). In addition, many instruments with high resolution and sensitivity are available (e.g., see "Hybrid Instruments" section starting on page 365).

Response

9. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection might have been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue that Stemmer is not prior art for the reasons set forth above (e.g., see 10/18/07 Response, page 24, section D).

[1] The Examiner respectfully disagrees for the reasons set forth in the 35 U.S.C. § 102 response, which is incorporated in its entirety herein by reference.

[2] Applicants argue that Favretto et al. "does not render the claimed invention obvious" (e.g., see 10/18/07 Response, page 24, section D).

[2] Applicant's arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references. Here, Applicants fail to explain why Favretto et al. does not render the claimed invention obvious.

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

Allowable subject matter

10. Claims 3, 26, 72, 73, 77, 106, 115, 119, 125, 127-143 are allowed. The following is a statement of reasons for the indication of allowable subject matter: The current claims are allowed for the reasons of record (e.g., see 11/3/06 allowance and arguments with respect to Abersold et al., which is the closest prior art). That is, the presently allowed claims disclose methods for performing high throughput mass spectrometry screening of cell culture components using electrospray tandem mass spectroscopy without requiring chromatographic separation of said samples prior to injection into the mass spectrometer. The prior art for the does not suggest such a method without the use of a chromatographic separation step. Benefit of the claimed method is its increased efficiency vis a vis the closest prior art, which employs slower chromatographic separations.

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Jon D. Epperson/
Primary Examiner, AU 1639